Severe Anaphylactic Reaction to Thiopentone: Case Report*

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In view of the estimated millions of thiopentone injections given annually, and the frequent reports of cutaneous manifestations of allergy to barbiturate drugs, it is surprising that anaphylaxis to barbiturates is so rarely reported. We believe that some cases may be unrecognized or misdiagnosed.

Case Report

A woman of 58 with carcinoma of the bladder had been treated seven years previously, in 1958, by transurethral resection. Thereafter at intervals of six months she had had 10 cystoscopic examinations, occasionally with diathermy of the bladder. General anaesthesia on each occasion had consisted of intravenous thiopentone, nitrous oxide, oxygen, and volatile supplement, and had been uneventful. In September 1964 the patient "collapsed" in a private hospital after a routine cystoscopy under general anaesthesia, which had included intravenous thiopentone, 0.5 g. The premedication was papaveretum, 20 mg., and atropine, 0.6 mg. She had remained unconscious for six hours, during which time she was given atropine, 1.2 mg., methoxamine, 20 mg., and metaraminol, 5 mg. intravenously and 10 mg. intramuscularly.

The present anaphylactic episode occurred in March 1965. Pre-operative examination had shown a robust woman who gave no history of reactions to drugs, but she stated that she had received an "overdose" during the previous anaesthesia. She was pre-medicated 90 minutes pre-operatively with pethidine, 50 mg., and hyoscine, 0.4 mg. Anaesthesia was induced cautiously with intravenous thiopentone. After 0.25 g. an unsuccessful attempt to lift the legs into the lithotomy position indicated that anaesthesia was too light, and a further 0.1 g. of thiopentone was given. It was then noticed that the patient had become cyanosed, the radial pulse was impalpable, and there was moderate bronchospasm. The lungs were gently inflated by assisted ventilation with halothane and oxygen, and the cystoscopy was completed after a further 10 minutes. Oxygen was given intranasally, and she was observed for 15 minutes. The peripheral pulses were impalpable, and the blood-pressure was unrecordable. The pupils remained small. During the next 10 minutes metaraminol was given intravenously, 1 mg. at a time to a total of 5 mg.; then the pulse became palpable at a rate of 168 per minute, and the systolic blood-pressure recordable at 75 mm. of mercury. Hydrocortisone sodium succinate, 100 mg., was given intravenously, and again eight hours later. She regained consciousness three hours after induction, but metaraminol, 5 mg. intramuscularly, was needed two-hourly for 12 hours to maintain the systolic blood-pressure above 80.

After 12 hours, despite her intense and sustained vasoconstriction, she was eating normally, and by the next day she had a warm pink skin, normal cerebation, and good secretion of urine, indicating full recovery. She then revealed that she had refused a sleeping-pill on the night before operation, because on the previous admission to hospital a quinalbarbitone capsule appeared to have caused "an itchy rash from head to foot." It was therefore concluded that this patient had become sensitive to barbiturates, and that on two occasions the intravenous injection of thiopentone had precipitated anaphylaxis.

Immunological Tests

Patch tests performed with pieces of gauze impregnated with 1% thiopentone, 5% pentobarbitone, and 10% sodium hexobarbitone gave immediate urticarial reactions. Similar patch tests with cyanocobalamin and 2.5% chlorpromazine were negative; these non-barbiturate drugs were chosen for control testing because they were readily available and known to be non-irritant to the skin. All patch tests were negative in one female control patient of the same age.

Intradermal injection of a 10^{-6} dilution of thiopentone produced, after 10 minutes, a weal 0.8 cm. in diameter surrounded by an area of erythema. A 10^{-7} dilution of thiopentone gave a weaker reaction, and a 10^{-8} dilution caused no reaction. Similar weal and flare reactions were obtained with pentobarbitone and sodium hexobarbitone in greater concentrations. No reaction was obtained with chlorpromazine and cyanocobalamin. The control subject showed no reaction to any test.

A passive transfer (Prausnitz-Küstner) test was performed by injecting the patient's serum, and serum from a normal control subject, intradermally into four sites on each forearm of two recipients. After 24 hours thiopentone, pentobarbitone, sodium hexobarbitone, and diluent were injected into the same areas. At the sites where the patient's serum had been injected a response to the barbiturates occurred in the form of a weal and flare reaction, which was maximal at 30 minutes. No reactions occurred at the areas into which serum from the control subject had been injected. Thus the patient's serum contained antibody to barbiturate of reagin type, presumably immunoglobulin A.

Passive cutaneous anaphylaxis was not induced in any one of three guinea-pigs; only thiopentone was used in the attempt to demonstrate this.

A gel-diffusion test in an Ouchterlony plate showed no precipitin lines when various solutions of thiopentone, pentobarbitone, and sodium hexobarbitone were tested against the patient's serum, and there was no *immune precipitate formation* when the serum of the patient was tested against various dilutions of thiopentone, pentobarbitone, and sodium hexobarbitone. Thus we were unable to demonstrate classical precipitating immunoglobulin G antibody to barbiturates in this patient's serum.

Management

A desensitization programme was not feasible because the patient came from a remote country district. She was therefore instructed to avoid all barbiturates, to carry an explanatory letter, and to wear always a specially made metal medallion bearing the inscription "Barbiturate hypersensitivity: Thiopentone anaphylaxis."

Discussion

Various cutaneous allergic reactions to barbiturates have been reported, including urticaria (Hunter, 1943; Knauss, 1946; Peterkin, 1946; Warren, 1946; Moore, 1946), scarlatiniform rash with pyrexia (Davison, 1943; Lemere *et al.*, 1952), photosensitivity (Evans and Gould, 1952), and severe exfoliative dermatitis (Welton, 1950). Welton's case also showed marked eosinophilia and severe hepatitis, both of which were attributed to phenobarbitone hypersensitivity. On the other hand, only three, or possibly four, cases of anaphylactic reaction to thiopentone have been reported in the literature available to us.

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Hayward and Kiester (1957) described the case of a dairy farmer aged 23 in whom a three-month episode of intractable hives had followed two injections of penicillin. His urticarial rash was thought to be perpetuated by penicillin in the cattle and poultry-food which he handled. A thiopentone anaesthetic for the extraction of several carious teeth precipitated a severe anaphylactic reaction with hypotension, laryngospasm, massive urticaria, and delayed return to consciousness. Intradermal skin tests with barbiturates, penicillin, and various grasses were positive.

Kivalo *et al.* (1960) described the case of a woman aged 32 who had shown a severe reaction, with unconsciousness, to a "sleeping-draught" and massive urticarial reactions attributed to penicillin sensitivity. During a laparotomy for sterility she had an anaphylactic reaction to thiopentone similar to that recorded by Hayward and Kiester (1957), but intradermal tests to barbiturates were negative.

Strunk (1962) reported the case of a man aged 39 whose history was similar to that of our patient. He had 10 uneventful thiopentone anaesthetics, and on the eleventh occasion it was proposed to resect the upper pole of his right kidney for renal calculus and pyonephrosis. Premedication consisted of pethidine and atropine. Thiopentone, 425 mg., given intravenously, produced sudden hypotension with an impalpable pulse, an unrecordable blood-pressure, a red coloration of the skin, and vomiting. He improved when given phenylephrine and hydrocortisone intravenously. He awakened 40 minutes after the induction of anaesthesia and his radial pulse and blood-pressure became detectable 90 minutes later at 140 per minute and 90/80. He had fully recovered after one day. There was a positive intradermal reaction to a 0.25% solution of thiopentone. It is of interest that each of the above three patients was subsequently anaesthetized uneventfully with a non-barbiturate anaesthetic.

A possible fourth case of barbiturate anaphylaxis was described as "collapse under Pentothal sodium anaesthesia" by Hoenigsberger (1943). This patient, a man aged 40, had a history of previous "collapse under general anaesthesia" and was operated upon for a compound fracture of the tibia and fibula and a fractured neck of the femur. After an injection of thiopentone, 0.6 g., he had a cardiac arrest, which eventually responded to artificial respiration and two intracardiac injections of adrenaline, 1 mg. Hypovolaemia may have contributed to the cardiac arrest, since the injury was severe enough to require an above-knee amputation three weeks later; for the latter operation he was given a unilateral procaine subarachnoid block. Tests for barbiturate sensitivity were not done.

The hazards of thiopentone anaesthesia are discussed in two reviews of anaesthetic deaths. Edwards *et al.* (1956) stated that 107 out of 1,000 "anaesthetic deaths" were associated with "circulatory failure" which immediately followed the intravenous injection of barbiturate; of these 107 cases 102 were described as "poor" or "very poor" anaesthetic risks because of heart or lung disease. Dinnick (1964) analysed 600 anaesthetic deaths and re-emphasized the hazard of thiopentone in association with hypovolaemia, since thiopentone in relative excess is known to cause profound hypotension. On the other hand, anaphylaxis to anaesthetic agents, including thiopentone, is not mentioned in either of these two reviews, nor in the standard textbooks of anaesthesia. Our present case leads us to suggest that some cases of unexplained hypotension, "collapse," or even death after induction of anaesthesia with thiopentone were due to an unrecognized anaphylactic reaction.

We would emphasize that, contrary to earlier views, anaesthesia itself does not protect against fatal anaphylaxis. Parish *et al.* (1963) showed that guinea-pigs sensitized to milk and thereafter anaesthetized with various agents, including halothane, ether, nitrous oxide, oxygen, trichlorethylene, and

pentobarbitone sodium, had a 100% mortality when challenged by the milk antigen intravenously.

We therefore advise anaesthetists to ask patients whether they have had allergic diseases or previous reactions to drugs; if so, patch tests and intradermal tests should be done to exclude hypersensitivity to anaesthetic drugs, particularly barbiturates. Where there is evidence of specific sensitivity, barbiturate anaesthesia must be avoided.

Effective emergency treatment of anaphylaxis is important. The administration of oxygen and an intravenous vasoconstrictor drug was followed by eventual recovery in each of the reported cases of thiopentone anaphylaxis. However, we believe that the intravenous administration of adrenaline or isoprenaline in high dilution might be more appropriate in augmenting cardiac output and diminishing bronchial spasm without intensifying systemic vasoconstriction. Other measures should include oxygen, an antihistamine drug such as promethazine, and hydrocortisone.

Summary

The case of a 58-year-old woman who twice developed a severe anaphylactic reaction to intravenous thiopentone is described. This hazard of general anaesthesia is not well known, because we found only three reported cases of anaphylactic reaction to thiopentone. Our patient resembled one of the reported cases in that hypersensitivity developed after 10 previous uneventful thiopentone anaesthetics. The diagnosis of anaphylaxis was confirmed by the demonstration of immediate cutaneous reagin-type hypersensitivity reactions to thiopentone and a positive passive transfer (Prausnitz-Küstner) reaction.

ADDENDUM.—On 28 March 1966 the subject of the above paper was uneventfully anaesthetized with propanidid 0.5 g., nitrous oxide, oxygen, and halothane.

ADDENDUM No. 2.—We have since observed a second case of anaphylaxis in a 26-year-old woman who "collapsed" on two occasions after injection of succinylcholine. The diagnosis of hypersensitivity to succinylcholine was confirmed by the demonstration of reagin-type antibodies in the serum of our patient (Jerums, G., Whittingham, S. F., and Wilson, P. (1966). In preparation.)

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